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NF-kB shuttling patterns in single cells:

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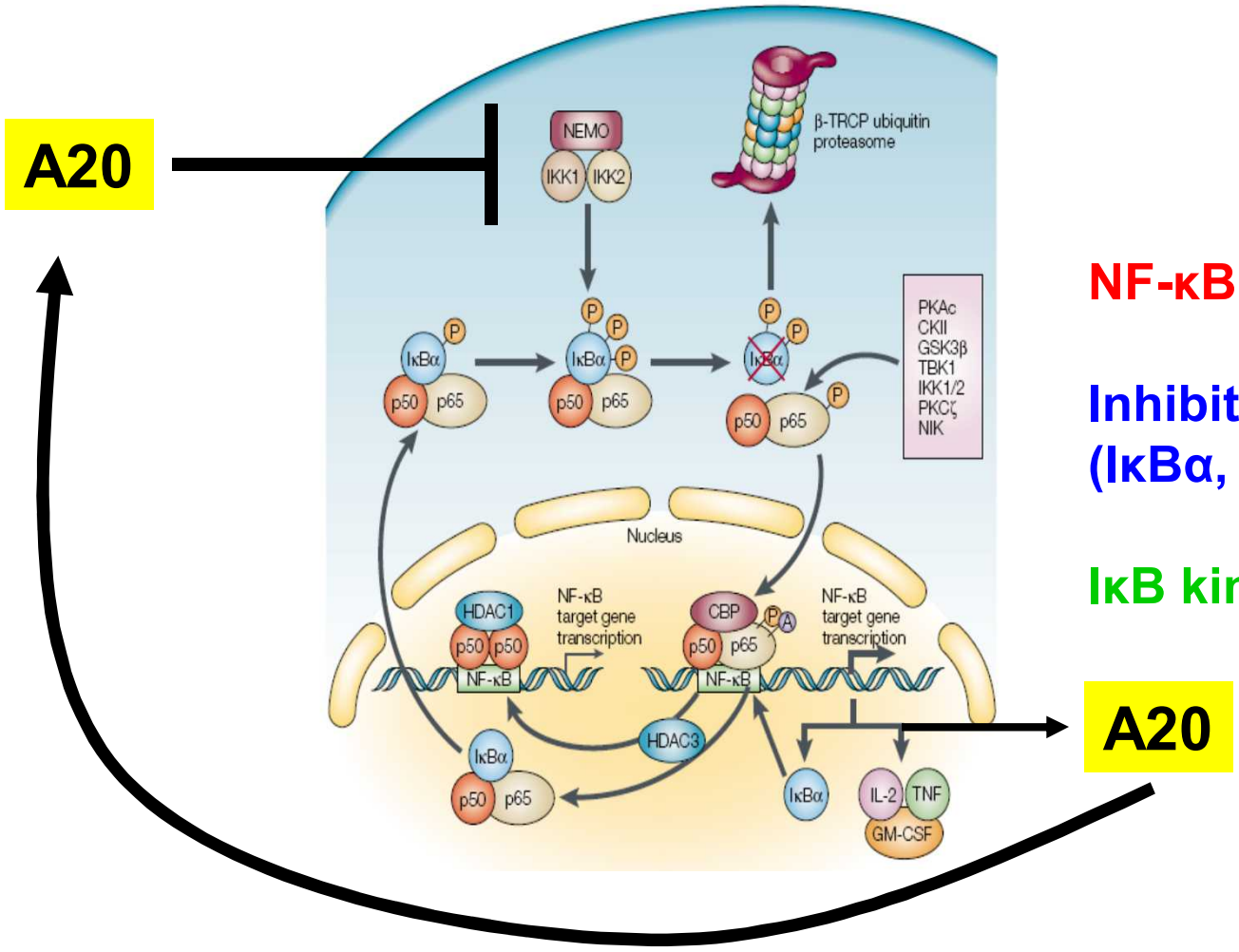
Overview of NF-κB signal transduction network



NF-κB (p65:p50)

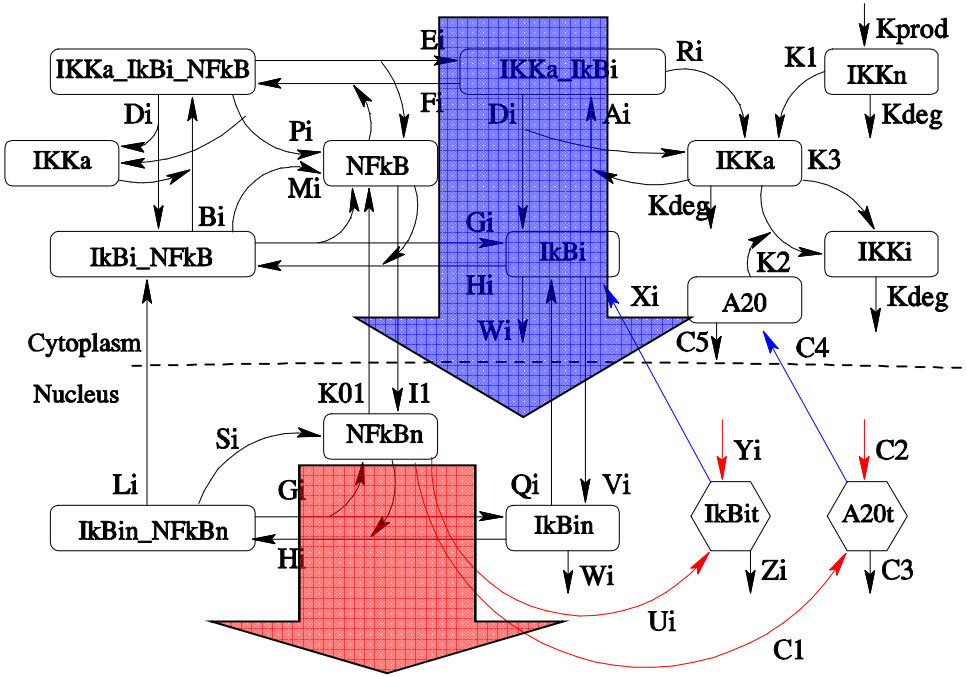
Inhibitor κB (IκBα, IκBβ, IκBε)

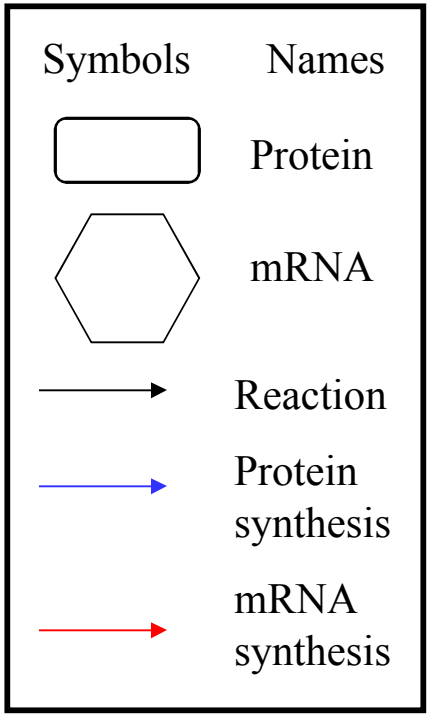
IκB kinase (IKK)

Nature Rev. Immunol. 2:725 (2002)

Latin Hypercube Sampling of input parameters

Input: Sampling of kinetic rate variables





Output: Distribution of dynamic features of nuclear NF- κB response

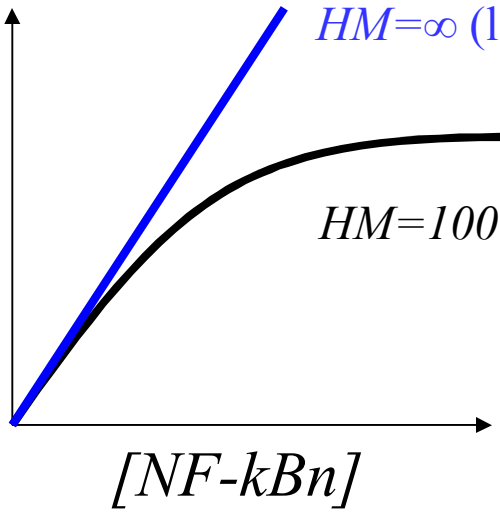
- **Latin Hypercube sampling** of 71 input variables (70 kinetic rates & 1 I.C.) uniformly from an interval (xo (1-f), xo (1+f)) where xo is a nominal value and f =70%
- Typical sample size: 1,000 to 10,000 ODE simulations

Transcription model

$$\text{DNA} + [NF\text{-}kBn] \underset{K_{OFF}}{\overset{K_{ON}}{\rightleftharpoons}} \text{DNA}^* \xrightarrow{C_1} \text{DNA} + [NF\text{-}kBn] + \text{mRNA}$$

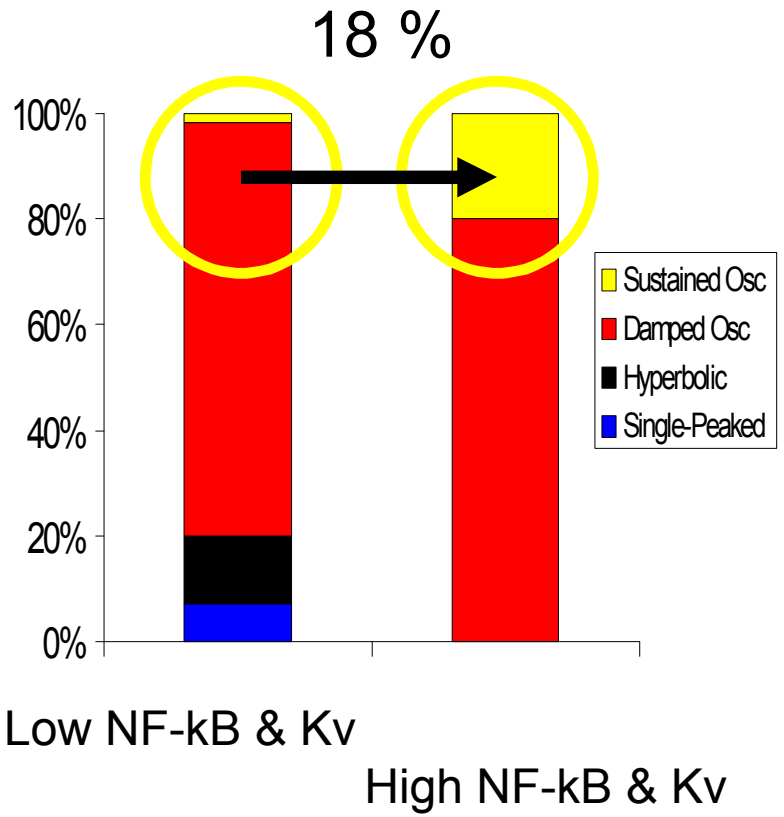
$$[NF\text{-}kBn] \xrightarrow{C_1^{eff}} [NF\text{-}kBn] + \text{mRNA}$$

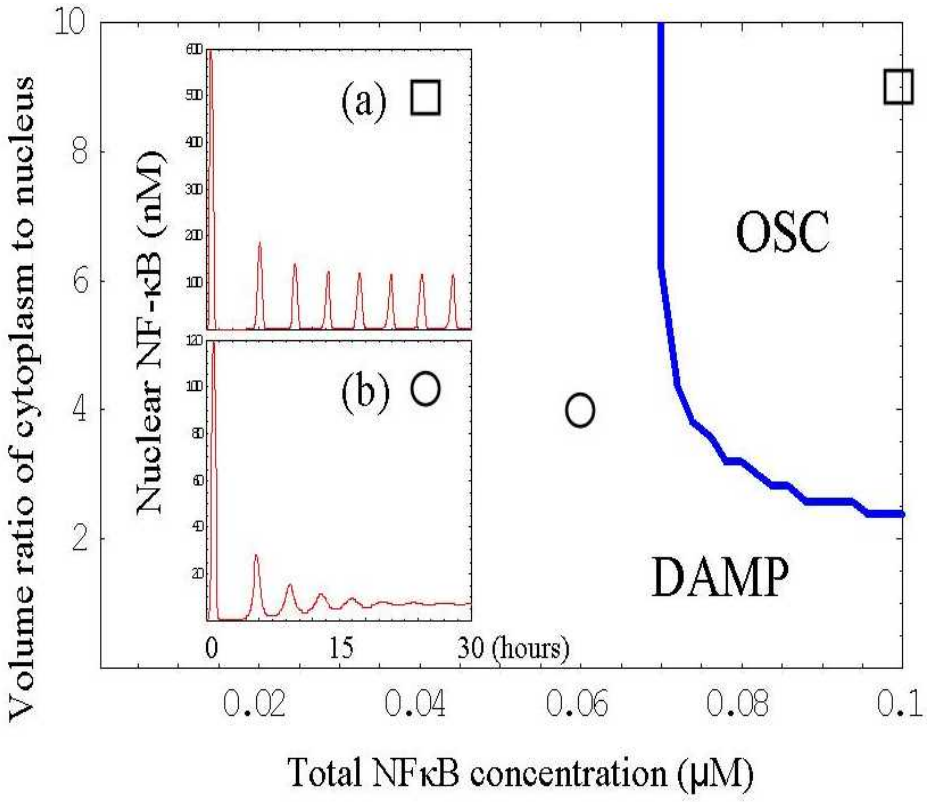
$$C_1^{eff} = \frac{C_1 \cdot HM \cdot [NFkBn]}{HM + [NFkBn]}$$



$$HM = \frac{K_{OFF}}{K_{ON}}$$

Total NF-κB & volume ratio dependent "phase transitions" of NF-κB shuttling patterns (HM=∞)



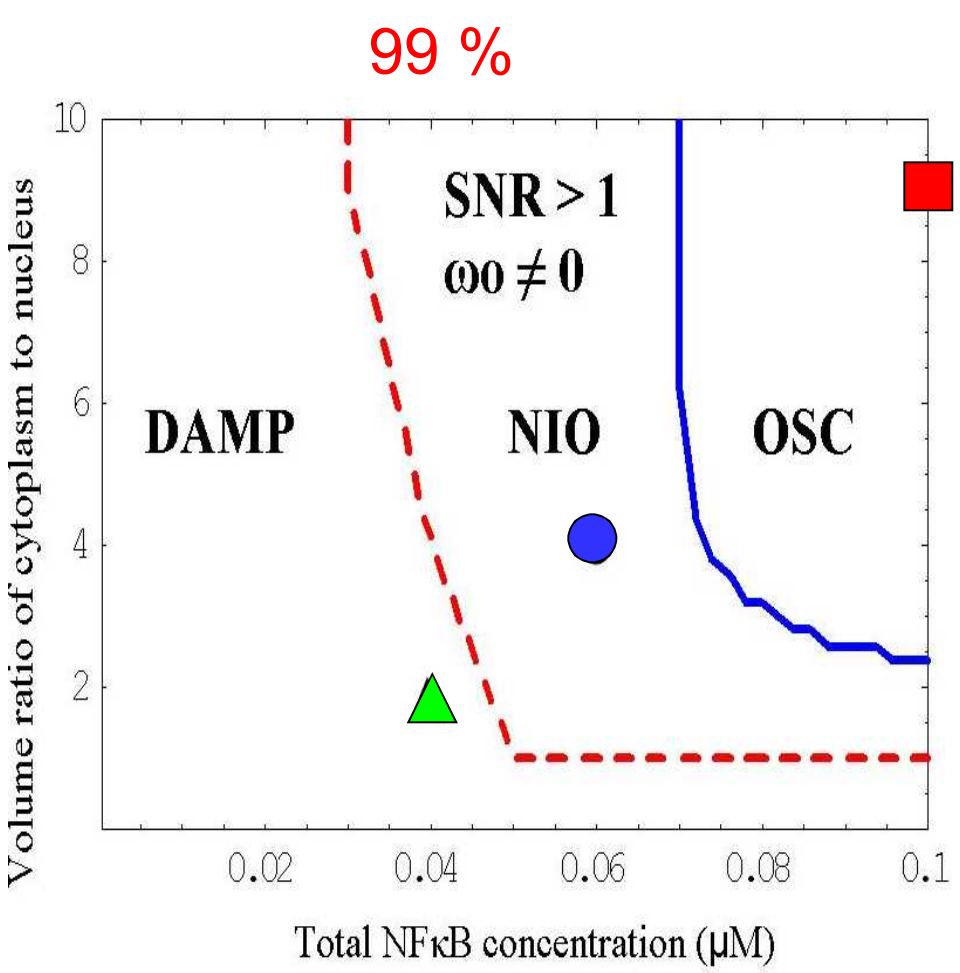


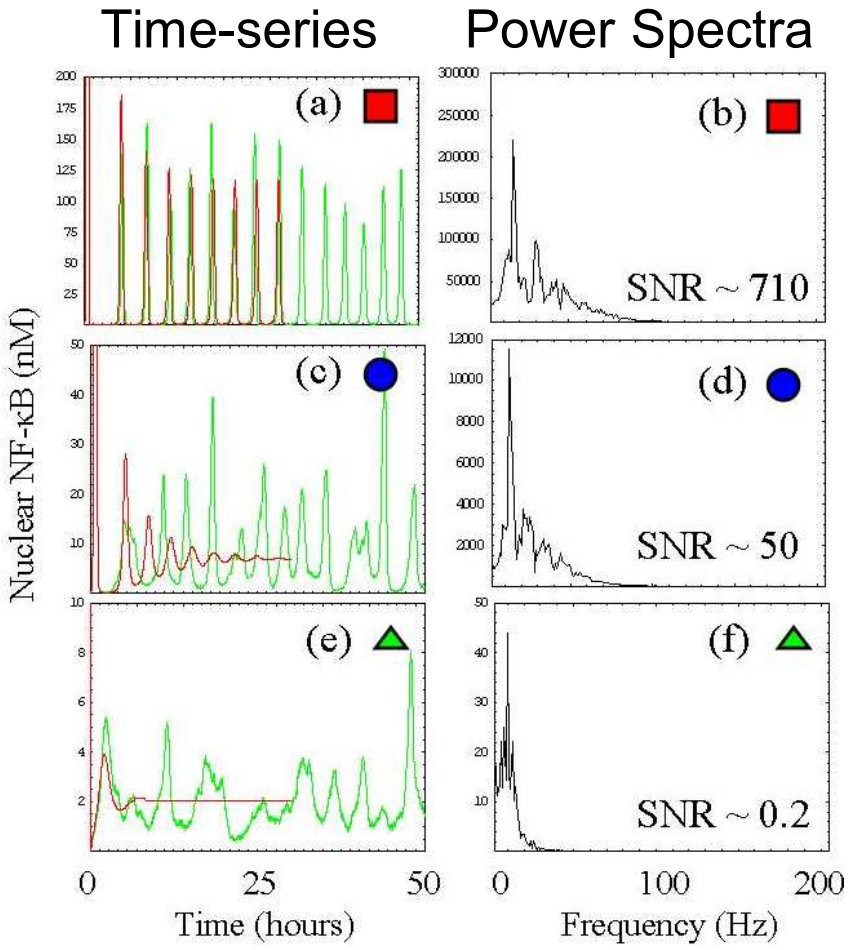
DAMP: Damped oscillation
OSC: Sustained oscillation

$$HM = \frac{K_{OFF}}{K_{ON}}$$

j4

Noise-induced oscillatory NF-κB shuttling (HM=∞)





DAMP: Damped oscillation
NIO: Noise-induced oscillation
OSC: Sustained oscillation

Criteria for noise-induced oscillation:

$$SNR = \frac{Peak\ Amplitude\ of\ P(\omega)}{\sqrt{Total\ NFkB}} > 1$$

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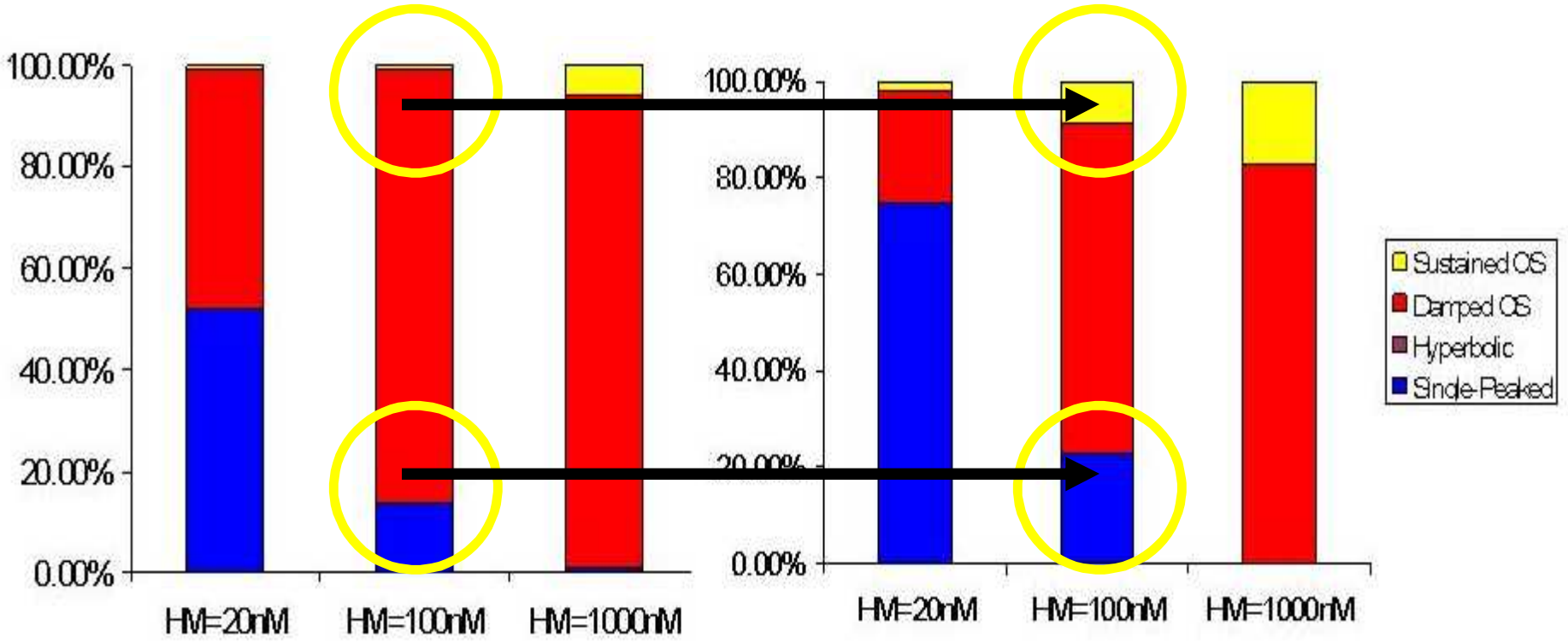
j4

The left phase diagram is only obtained from 18 % of the kinetic conditions. But, the stochastic system results in transition from DAMP to NIO as two variables are changed from low to high values at almost 99 % of kinetic conditions.

jjoo, 1/14/2008

Total NF-κB & volume ratio dependent "phase transitions" of NF-κB shuttling patterns



Low NF-kB & Kv

High NF-kB & Kv

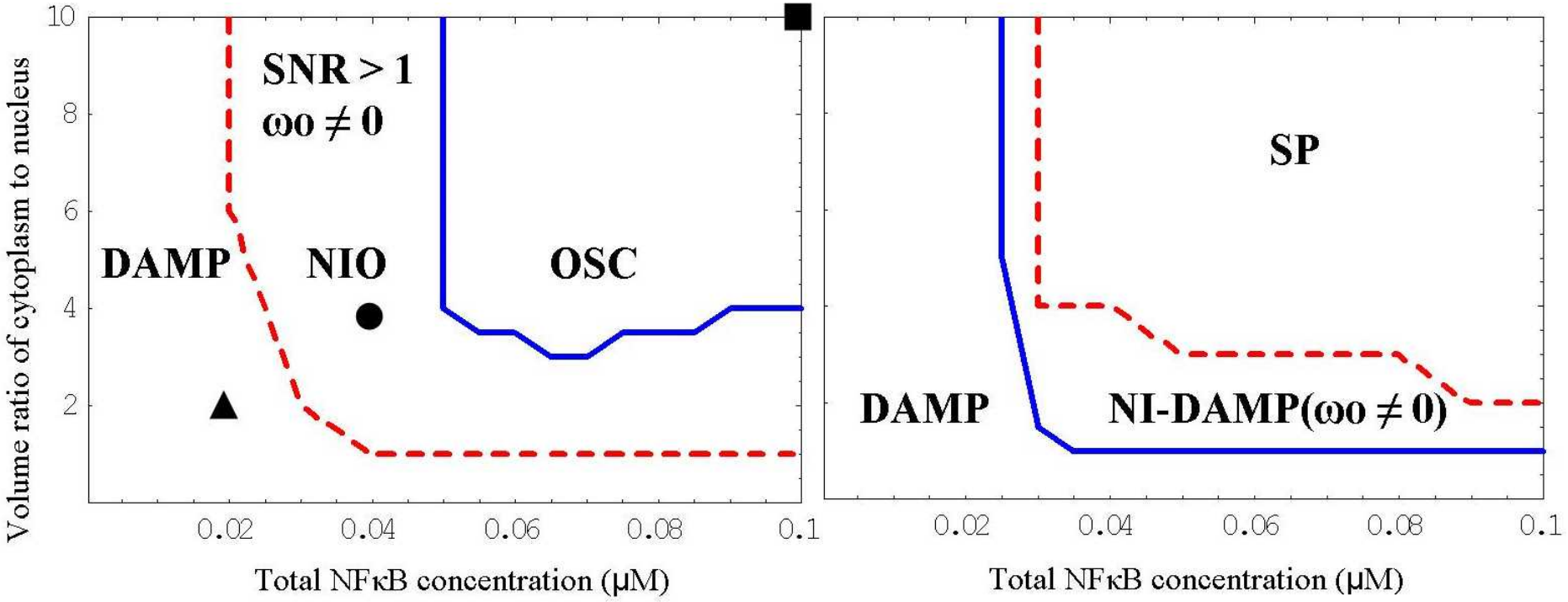
$$HM = \frac{K_{OFF}}{K_{ON}}$$

j3

Noise-induced phase transitions of NF-κB shuttling (HM=100 nM)

30 %

9 %



Unchanged phases:
SP 14 %
DAMP 46 %
OSC 1 %

DAMP: Damped oscillation
NIO: Noise-induced oscillation
OSC: Sustained oscillation
SP: Single-peaked pattern
NI-DAMP: Noise-induced damped oscillation

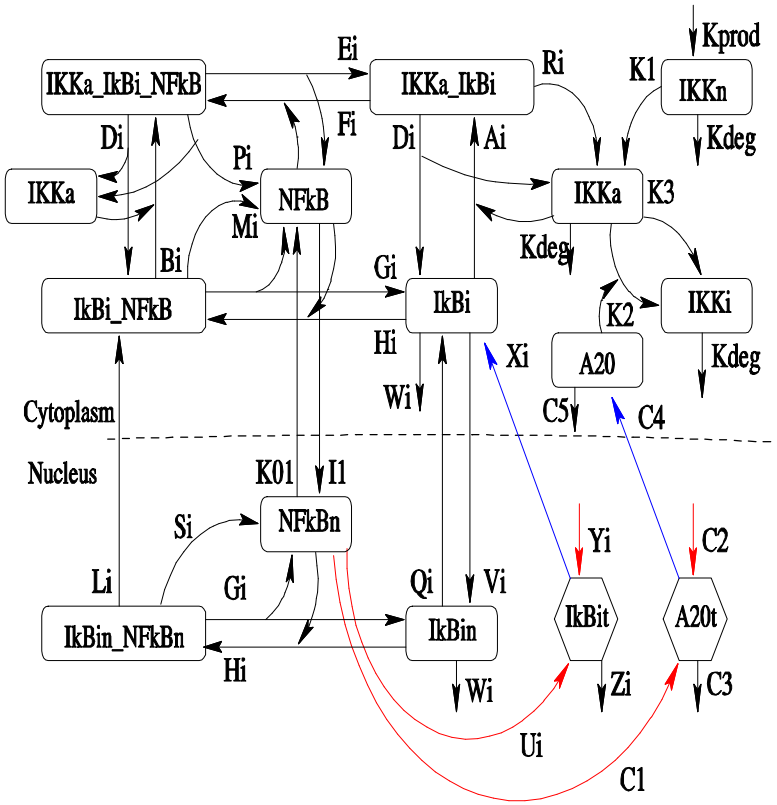
$$HM = \frac{K_{OFF}}{K_{ON}}$$

Slide 8

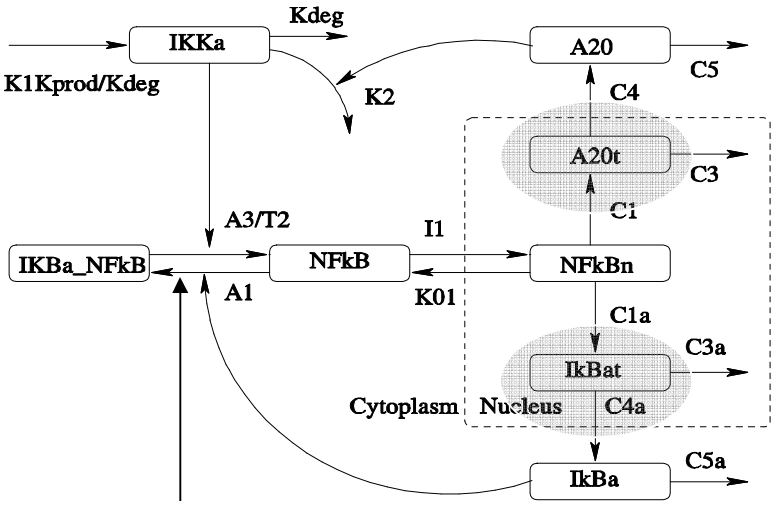
j3 The left sided phase diagram is obtained out of 8% of kinetic conditions. However, When the 30 % of the same kinetic conditions yield the transition from the DAMP to the NIO as two variabels are changed from low to high values. This is why I denote 30% instead of 8%.

Likewise, for the unchanged phases, DAMP is 68 % with deterministic system but it is changed to 46 %.
jjoo, 1/14/2008

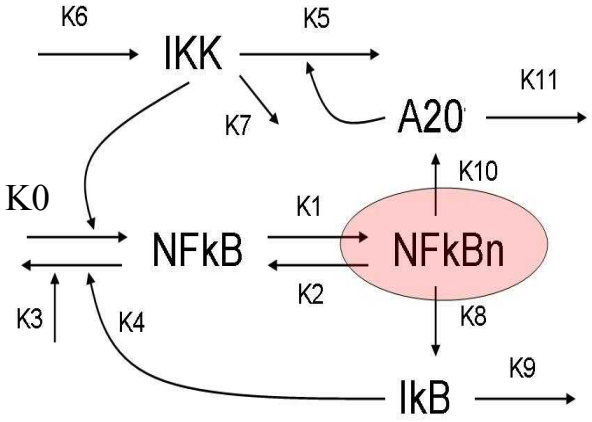
Reduction of full model to minimal model: Renormalization of kinetic rate variables



Full Model



Intermediate Model



Minimal Model

Linear Fokker Planck equation for stochastic minimal model

$$\frac{d\Pi(\vec{\xi};t)}{dt} = -\sum_{\alpha}\frac{\partial A_{\alpha}\Pi}{\partial \xi_{\alpha}} + \frac{1}{2}\sum_{\alpha,\beta} B_{\alpha\beta}\frac{\partial^2\Pi}{\partial\xi_{\alpha}\partial\xi_{\beta}}$$

A_{α} is a linear function of $\vec{\xi}$: $A_{\alpha} = \sum_{\beta} M_{\alpha\beta}\xi_{\beta}$

M is a matrix without $\vec{\xi}$.

B is a noise covariance matrix and responsible for noise amplifiaction.

Equivalence of linear FP equation with Langevin equation :

$$\frac{d\vec{\xi}(t)}{dt} = \mathbf{M}\cdot\vec{\xi}(t) + \eta(\mathrm{t}); \qquad \left\langle \eta_{\alpha}(t)\eta_{\beta}(t')\right\rangle = B_{\alpha\beta}\delta(t-t')$$

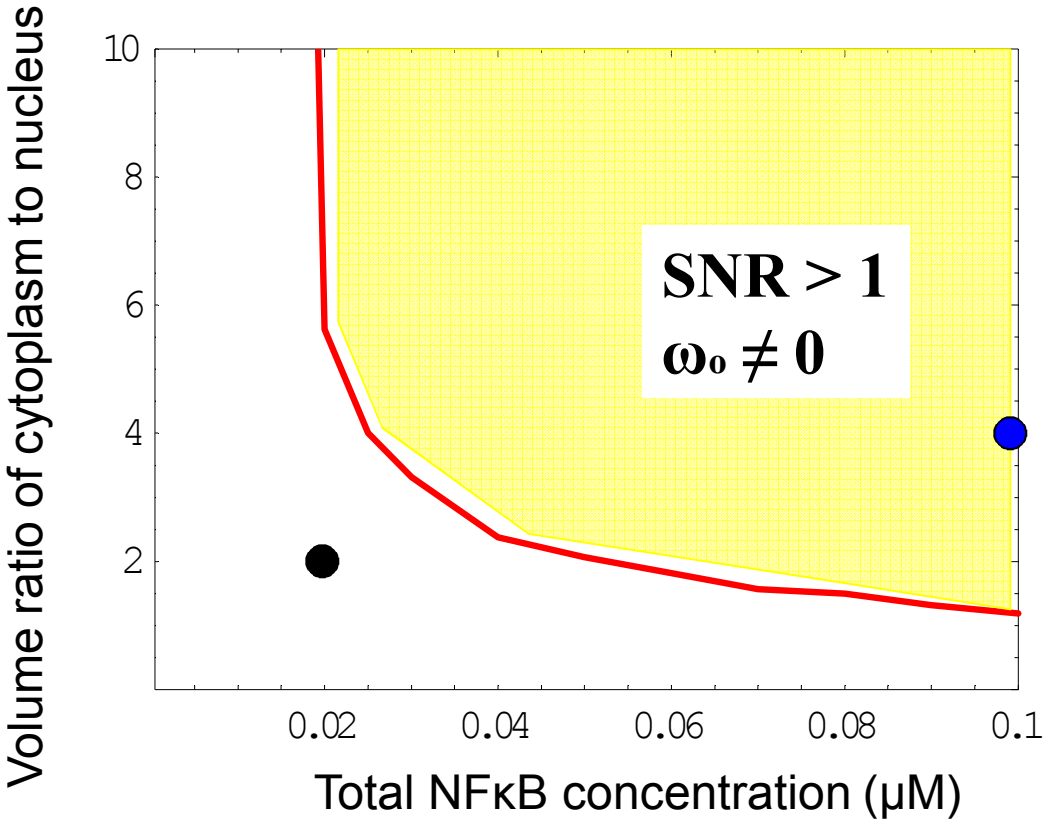
Power Spectrum :

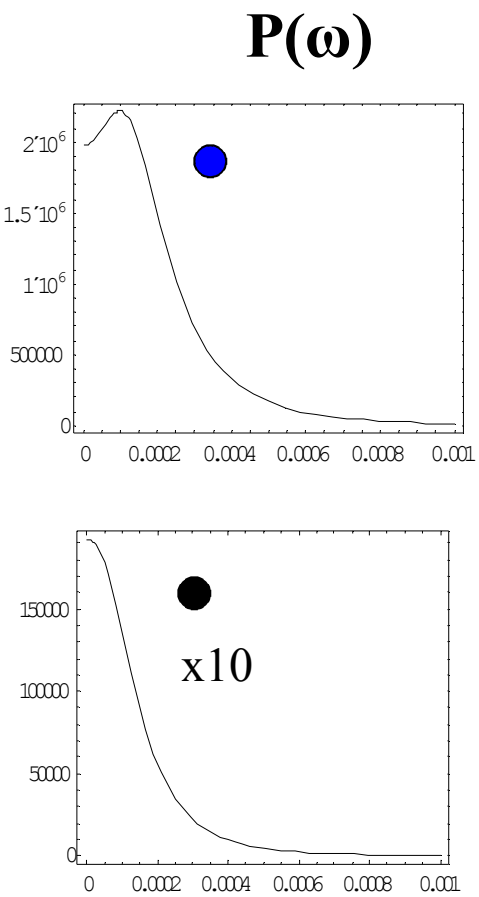
$$P_{\alpha}(\omega) = \left\langle \xi_{\alpha}(\omega)\xi_{\beta}^{*}(\omega)\right\rangle$$

$$= \sum_{\beta,\gamma}(-i\omega\mathbf{E} - \mathbf{M})^{-1}_{\alpha\beta} B_{\beta\gamma}[(-i\omega\mathbf{E} - \mathbf{M})^{-1}]^{*}_{\gamma\alpha}$$

We calculate power spectrum from **M** and **B**.

Noise-induced oscillatory domain: stochastic minimal model





- Deterministic minimal model: a single stable fixed point
- Stochastic minimal model: amplification of noise-induced oscillation for high NFkB conc. and volume ratio.

Conclusion

1. Sensitivity analysis reveals that the NF-κB dynamics critically depends on total NF-κB concentration and volume ratio of cytoplasm to nucleus.
2. Deterministic full hybrid model generates the dynamic instability when both total NF-κB concentration and volume ratio are large.
3. Noise expands the instability domain of NF-κB, i.e., emergence of noise-induced oscillation of NF-κB at its natural frequency.
4. Stochastic minimal model qualitatively reproduces the noise-induced oscillation of NF-κB whereas its deterministic counterpart has only stable fixed point.

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